Editing of Parkinson's disease mutation in patient-derived iPSCs by zinc-finger nucleases

Grant Award Details

Editing of Parkinson's disease mutation in patient-derived iPSCs by zinc-finger nucleases

Grant Type: Tools and Technologies II

Grant Number: RT2-01965

Project Objective: The fundamental rationale underlying this grant is the combination of two new technologies, with which the team can establish isogenic cellular tools to explore disease mechanisms, carry out gene repair, and develop novel platforms for drug discovery. They are using the most common LRRK2 G2019S mutation for Parkinson's Disease as a proof of principle.

Investigator:

Name:	Birgitt Schuele
Institution:	Parkinson's Institute
Type:	PI

Disease Focus: Parkinson's Disease, Neurological Disorders

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,327,983

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4/NCE

View Report

Grant Application Details

Application Title: Editing of Parkinson's disease mutation in patient-derived iPSCs by zinc-finger nucleases

Public Abstract: The goal of this proposal is to establish a novel research tool to explore the molecular basis of Parkinson's disease (PD) - a critical step toward the development of new therapy. To date, a small handful of specific genes and associated mutations have been causally linked to the development of PD. However, how these mutations provoke the degeneration of specific neurons in the brain remains poorly understood. Moreover, conducting such genotype-phenotype studies has been hampered by two significant experimental problems. First, we have historically lacked the ability to model the relevant human cell types carrying the appropriate gene mutation. Second, the genetic variation between individuals means that the comparison of a cell from a disease-carrier to a cell derived from a normal subject is confounded by the many thousands of genetic changes that normally differentiate two individuals from one another. Here we propose to combine two powerful techniques – one genetic and one cellular – to overcome these barriers and drive a detailed understanding of the molecular basis of PD. Specifically, we propose to use zinc finger nucleases (ZFNs) in patient-derived induced pluripotent stem cells (iPSC) to accelerate the generation of a panel of genetically identical cell lines differing only in the presence or absence of a single disease-linked gene mutation. iPSCs have the potential to differentiate into many cell types – including dopaminergic neurons that become defective in PD. Merging these two technologies will thus allow us to study activity of either the wild-type or the mutant gene product in cells derived from the same individual, which is critical for elucidating the function of these disease-related genes and mutations. We anticipate that the generation of these isogenic cells will accelerate our understanding of the molecular causes of PD, and that such cellular models could become important tools for developing novel therapies.

Statement of Benefit to California: Approx. 36,000-60,000 people in the State of California are affected with Parkinson's disease (PD) – a number that is estimated to double by the year 2030. This debilitating neurodegenerative disease causes a high degree of disability and financial burden for our health care system.

Importantly, recent work has identified specific gene mutations that are directly linked to the development of PD. Here we propose to exploit the plasticity of human induced pluripotent stem cells (iPSC) to establish models of diseased and normal tissues relevant to PD. Specifically, we propose to take advantage of recent developments allowing the derivation of stem cells from PD patients carrying specific mutations. Our goal is to establish advanced stem cell models of the disease by literally "correcting" the mutated form of the gene in patient cells, therefore allowing for direct comparison of the mutant cells with its genetically "repaired" yet otherwise identical counterpart. These stem cells will be differentiated into dopaminergic neurons, the cells that degenerate in the brain of PD patients, permitting us to study the effect of correcting the genetic defect in the disease relevant cell type as well as provide a basis for the establishment of curative stem cells therapies.

This collaborative project provides substantial benefit to the state of California and its citizens by pioneering a new stem cell based approach for understanding the role of disease causing mutations via "gene repair" technology, which could ultimately lead to advanced stem cell therapies for Parkinson's disease – an unmet medical need without cure or adequate long-term therapy.

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